Published in final edited form as:

Mov Disord. 2013 June 15; 28(7): 889–898. doi:10.1002/mds.25549.

ASSESSMENT OF THE PATIENT WITH ISOLATED OR COMBINED DYSTONIA: AN UPDATE ON DYSTONIA SYNDROMES

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Abstract

The clinical evaluation of a patient with dystonia is a stepwise process, beginning with classification of the phenomenology of the movement disorder(s), then formulation of the dystonia syndrome, which in turn leads to a targeted etiological differential diagnosis. In recent years there have been significant advances in our understanding of the etiological basis of dystonia, aided especially by discoveries in imaging and genetics. In this article, we provide an update on the assessment of a patient with dystonia, including the phenomenology of dystonia and highlighting how to integrate clinical, imaging, blood and neurophysiological investigations in order to formulate a dystonia syndrome. Evolving or emerging dystonia syndromes are reviewed and potential etiologies of these as well as established dystonia syndromes listed in order to guide diagnostic testing.

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Prof Vidailhet has no relevant disclosures

The authors report no relevant conflicts of interest regarding this research.

Funding sources for the study:

Nil

Keywords

diagnosis; phenomenology; etiology; differential diagnosis; secondary dystonia

Introduction

The clinical evaluation of a patient with dystonia is a stepwise process, beginning with classification of the phenomenology of the movement disorder(s), then formulation of the dystonia syndrome, which in turn leads to a targeted etiological differential diagnosis (Table 1) (1–6). In recent years there have been significant advances in our understanding of the etiological basis of dystonia, aided especially by discoveries in imaging and genetics. Careful clinical evaluation of patients with distinct radiological or genetic characteristics has in turn led to new ways of thinking about the growing list of disorders where dystonia may be isolated or combined with other clinical features.

As the number of dystonia syndromes and recognized etiologies have grown, the diagnostic approach has become increasingly challenging. A “shotgun” approach that involves testing for all potential disorders is not suitable for three reasons. First, the number of tests to consider is long, and it is rarely possible to test for everything. Second, some of the diagnostic tests are very expensive (such as genetic tests), making it important to select those that are most relevant. Third, some of the tests are invasive and uncomfortable (such as skin or bone marrow biopsy) and should be avoided unless necessary. Currently, there are no widely accepted guidelines for choosing which tests to conduct, and in what order. As a result, diagnostic habits vary widely, even amongst movement disorders specialists. Diagnostic testing can be guided by a strategy that involves a syndromic approach (7, 8). Briefly, the syndromic approach involves classifying patients according to accompanying clinical features, and tailoring the diagnostic studies to that syndrome. Our aim is to outline this strategy to assist the clinician when evaluating a patient with dystonia (Table 1).

Use of the term dystonia across different diagnostic levels

The term dystonia can be used to describe the phenomenology, clinical syndrome (e.g. “adult-onset focal dystonia”) with a number of potential etiologies, as well as the specific etiological diagnosis (4, 9). It is therefore necessary to specify the diagnostic level for which the term is being used (6).

Phenomenological diagnosis

Is it dystonia?

The updated Consensus Committee definition of dystonia is: “*Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.*” (5). The phenomenology of dystonia is discussed in detail elsewhere in this issue (6).

Is the dystonia isolated or combined with another movement disorder?

The next step in characterizing the phenomenology is to determine whether dystonia is the only movement disorder (isolated dystonia) or combined with another movement disorder (combined dystonia). There are two potential sources of error. The first is the misdiagnosis of dystonia as another movement disorder, leading to mislabeling a syndrome as being a combined rather than isolated dystonia. The second is the failure to recognize a second movement disorder that co-exists in a patient with dystonia, leading to mislabeling as an isolated rather than mixed movement disorder. Both these errors can lead to an incorrect syndromic diagnosis and therefore consideration of inappropriate etiological diagnoses.

The most common reason for the first error is the patient who presents with prominent phasic dystonia. Phasic dystonia can mimic many other movement disorders (e.g. tremor, tics). In the case of obvious underlying abnormal posturing, the clue that the associated phasic movement is dystonic is that it occurs in the same part of the body. However if phasic dystonia dominates, there may be only subtle stereotyped abnormal posturing in the body part(s) affected by the involuntary movements that provides the clue to its dystonic origin. The patient needs to be instructed to allow the involuntary movement to occur freely, as voluntary compensatory postures or movements can be misleading. For example, a latent abnormal posture underlying tremor-dominant cervical dystonia often can be revealed by asking the patient to relax with eyes closed and let the head drift where it feels most comfortable, a manoeuvre that often leads to unrecognized torticollis or laterocollis. Dystonic tremor is often more irregular in timing and amplitude than non-dystonic tremor, as the underlying muscle bursts tend to be irregular in duration and amplitude (10).

Avoidance of the second error requires the ability to recognize additional movement disorders when they coexist with dystonia. The features of dystonic compared with non-dystonic tremor have been alluded to above. In the case of chorea superimposed on dystonia, the clue is that chorea produces movements that vary randomly in duration, direction and amplitude (rather than movements that are patterned or stereotyped), and flow from one part of the limb or body to the other. Dystonia can cause rapid, jerky movements that can be confused with myoclonus. When myoclonus co-exists with dystonia, it will usually be present not only in parts of the body affected by dystonia, but also in non-affected parts. Athetosis is a movement disorder that occurs in the setting of dystonia and can be confused with tremor, chorea or myoclonus (11, 12). Athetosis at one stage became used synonymously with dystonia but as originally described by Hammond (12, 13) refers to repetitive movements of variable speed and frequency that independently affect individual but usually multiple fingers, toes and facial muscles. The importance of recognizing athetosis is that if misdiagnosed, it can lead to a patient misclassified as having a combined rather than isolated dystonia (see Dystonia Syndromes below). The recognition of pyramidal involvement in the setting of dystonia can sometimes be difficult. Hyper-reflexia can occur in dystonia, presumably due to reinforcement of reflexes from dystonic muscle activation, and plantar responses can appear extensor due to a striatal toe, mimicking a Babinski response (14). In spasticity, hypertonia is velocity-dependent whereas in dystonia, resting hypertonia is relatively uncommon and when present, tends to be more variable rather than velocity dependent (15). Hypertonia in spasticity often occurs at rest, and during walking

leads to the characteristic postures of exaggerated hip abduction, knee extension and ankle plantar flexion and inversion. While dystonic posturing can mimic this, it more commonly gives rise to other patterns. In spasticity, the severity of the abnormal posturing tends to be constant throughout the gait cycle while dystonic posturing often varies. For example, in a dystonic gait, the ankle might be inverted during the early swing phase but then normalize or even become everted just before the stance phase. Dystonic stiffness and posturing of the legs can improve significantly or even be absent during different walking tasks such as walking backwards, walking heel to toe, or running, whereas a spastic gait does not change significantly according to task.

Dystonia syndromes

A syndrome is a characteristic collection of symptoms and signs that tend to cluster together. A syndrome is sometimes unique to a single disease, but more commonly has multiple potential etiologies. However the identification of a syndrome limits the list of etiological differential diagnoses and is the next step after classifying the phenomenology in order to guide diagnostic investigations and/or management (Table 2). While many of these clinical features are readily recognized by most neurologists, some may require additional input from other types of physicians. Consultations may therefore be useful in ophthalmology, human genetics or other specialties. In patients with a progressive disorder, a full clinical evaluation should be repeated periodically as some symptoms and signs may be absent initially and will appear with age.

The importance of the dominant movement disorder

If dystonia is combined with other features, the next step is to decide upon the dominant phenomenology (2). For example, in the case of a familial movement disorder where dystonia is mild and there is severe spasticity, this might lead to a syndromic diagnosis of complicated hereditary spastic paraparesis with dystonia, with a limited list of etiological diagnoses, whereas if dystonia is dominant with milder spasticity, the syndromic diagnosis is combined dystonia with pyramidal involvement, with a much wider list of potential etiological diagnoses. While this approach to defining the dominant movement disorder helps to focus the diagnostic plan, it is important to recognize that many exceptions occur.

Additional neurological system involvement

A full history and examination are required to determine whether there are non-motor components of the syndrome. Of particular importance are ophthalmological symptoms or signs, which may suggest specific disorders. The presence of visual symptoms and dystonia mandate a formal ophthalmological examination to look for evidence of optic nerve or retinal abnormalities that are characteristic of some inherited metabolic diseases. Corneal abnormalities, in particular Kayser-Fleischer rings characteristic of Wilson's disease, can also be present. The presence of a supranuclear gaze palsy, and whether vertical, horizontal or both, can be a useful clue.

Another question is whether there is additional central nervous system involvement. Is there cognitive impairment or epilepsy in addition to the motor features? The presence or absence

of pyramidal involvement will already have been considered in the evaluation of the movement disorder, but is there evidence of other spinal cord sensory or autonomic involvement? Finally, is there peripheral nervous system involvement or myopathy?

Temporal evolution of neurological features

The significance of whether dystonia is static, progressive or intermittent has been highlighted recently (5). In the setting of multi-system neurological disease, the temporal sequence of problems can have diagnostic significance. The end-stage of many severe neurodegenerative diseases can appear similar, regardless of the starting features or etiology. Degenerative diseases primarily targeting grey matter are more likely to give rise to dystonia earlier, as well as dementia and epilepsy. Degenerative diseases primarily targeting white matter (leukoencephalopathies) are more likely to present with spasticity or ataxia. Certain diseases characteristically begin with a particular movement disorder with other neurological manifestations only occurring later. For example dopa-responsive dystonia secondary to GTP-cyclohydrolase deficiency (Segawa disease), usually manifests predominantly as dystonia in childhood but Parkinsonism becomes increasingly prominent with older age.

Systemic involvement

The neurologic assessment of a patient with dystonia should include a systemic examination, looking especially for the presence of organomegaly, which can indicate a storage disease, as well as skin, connective tissue or skeletal involvement. The presence of haematological or endocrine abnormalities can also be of significance (see below for more detailed discussion of dystonia syndromes with systemic features).

Dystonia syndromes: Integration of results of basic investigations

In the modern era, depending on the clinical syndrome, in many instances the first investigations are not necessarily aimed at a single diagnosis, but instead to further define the dystonia syndrome. Of these, cerebral imaging, particularly with MRI, and screening blood tests are essential as they may reveal abnormalities that cannot be ascertained by clinical assessment.

The importance of cerebral imaging

Although brain MRI is not necessary in most adult-onset focal dystonias, it should be considered in all early-onset cases (except perhaps cerebral palsy due to an established insult) and in all cases where dystonia is combined with other neurological features. The MRI should include iron-sensitive sequences. In addition to excluding dystonia due to focal lesions, relevant abnormalities present on cerebral MRI can be used to help define the dystonia syndrome, such as any basal ganglia abnormalities (e.g. increased signal, cystic degeneration, atrophy or evidence of abnormal iron deposition); abnormal signal or atrophy of the brain outside the basal ganglia; and the presence or absence of white matter disease. The presence of a normal MRI in the setting of a progressive isolated or combined dystonia also narrows the etiological possibilities. A cerebral CT can be more sensitive and specific at detecting basal ganglia calcification, but otherwise MRI is the investigation of choice.

Routine blood investigations

Routine investigations for almost all patients with combined dystonia syndromes should include a blood count looking for anemia, leucopenia, or thrombocytopenia, and at least an automated blood film to look for acanthocytes although examination of a wet smear, sometimes on multiple occasions, is required if there is a strong suspicion of neuro-acanthocytosis. Blood chemistry can identify early liver or renal disease. Iron studies, manganese, calcium and parathyroid hormone levels can also be useful, especially in patients with basal ganglia abnormalities on MRI. A high serum uric acid can point to Lesch-Nyhan disease, although it is not sensitive or specific enough to serve as a diagnostic test.

In any patient presenting with dystonia, the possibility of Wilson's disease should be considered. In two series which together included over 200 patients with neurological Wilson's disease (16, 17) the age at diagnosis was 7–39 years, but presentation in the seventh decade (18) and a genetically proven asymptomatic patient manifesting only Kayser-Fleischer rings in the ninth decade (19) have been documented. There are no evidence-based guidelines for diagnostic testing to exclude neurological Wilson's disease (20), but suggested investigations include serum copper and ceruloplasmin and ophthalmological slit lamp examination to look for Kayser-Fleischer rings (20), all of which may occasionally be normal. 24 hour urinary copper excretion and cerebral MRI are probably abnormal in all patients with neurological Wilson's (16, 21) but may not necessarily be specific for the disease. The most specific tests are liver biopsy with measurement of hepatic copper content and genetic analysis of the ATP7B gene (20).

Neurophysiological investigations

Neurophysiological tests such as nerve conduction studies (NCS) and somatosensory evoked potentials (SEPs) should be considered an extension of the neurological examination. In the setting of a progressive dystonia or where the sensory examination cannot be reliably assessed (e.g. infancy or in the presence of significant cognitive impairment) they are important in defining whether there is peripheral or central sensory involvement. In the case of progressive dystonia, a normal clinical sensory examination, even if reliable, is insufficient to exclude a neuropathy. SEPs can detect central sensory involvement or giant cortical potentials that may not have clinical manifestations.

Use of the dystonia syndrome to guide etiological differential diagnosis and investigations

The above section has described an approach to determine whether a patient has isolated or combined dystonia as the movement disorder, and whether there are other neurological or systemic manifestations. These are two of the five key descriptors of the clinical characteristics of dystonia, according to the new clinical classification (5). These five descriptors, together with the results of the basic investigations described above, can be used to generate a list of dystonia syndromes (Table 2). Each syndrome in turn generates a list of potential etiologies that can guide specific diagnostic tests or management.

For any individual with dystonia, the formulation of the dystonia syndrome needs to be tailored and to a certain extent depends on the weighting that the clinician places on each of the five descriptors of dystonia and/or results of investigations that are available. For example, isolated focal dystonia in childhood has a wide differential diagnosis and requires detailed investigation, whereas the same syndrome in adulthood is almost always a sporadic, idiopathic disease that does not progress to generalized dystonia and rarely heralds the onset of progressive neurological disease. Thus imaging in adult onset cervical dystonia has a very low diagnostic yield (22) and many would consider imaging in other forms of adult onset focal dystonia also unnecessary. Yet if a cerebral MRI was performed in a patient with adult onset focal dystonia and showed an abnormality such as an eye of the tiger sign that has a high specificity for pantothenate kinase associated neurological disease (PKAN) (23), further investigations would be warranted.

Some syndromes based on the movement disorder, or the presence of other neurological or systemic features, require extensive investigation regardless of age (7, 8), whereas in others, the age of onset has a significant influence on the differential etiological diagnosis and requirement for investigation.

Selected dystonia syndromes

The large number of dystonia syndromes makes it impossible to address them all in detail in a single article. We will therefore discuss selected syndromes that have been characterized relatively recently, either clinically, radiologically or genetically. A more comprehensive differential diagnosis of these syndromes as well as others listed in Table 2 are available as supplementary materials.

Isolated dystonia syndromes that are red flags for the subsequent development of a combined dystonia syndrome or neurodegenerative disease

Cranial dystonia in young adults and children—In older adults, isolated oromandibular dystonia is not uncommon, often combined with involvement of the upper face (“Meige syndrome”). Oromandibular dystonia in young adults and children most often occurs in the setting of generalized dystonia. Isolated oromandibular dystonia in young adults and children is distinctly unusual, and should raise concern that it is an early manifestation of what will evolve into a combined dystonia syndrome or neurodegenerative disease (7). Very prominent oromandibular dystonia may be particularly common in some disorders such as Lesch-Nyhan disease, glutaric aciduria, neuroacanthocytosis, and the neuronal brain iron accumulation (NBIA) disorders (24–26).

Limb dystonia—Dystonia that begins in one leg or one arm occurs in childhood-onset dystonia of various etiologies. In adults, upper limb dystonias are often task specific, such as writer’s cramp or musician’s dystonia. Isolated adult-onset lower limb dystonia is much less common although may also have varied etiologies (27, 28). Limb dystonias emerging in adults without task specificity, or those that rapidly lose task-specificity, should raise concern that they are a presenting sign of an underlying neurodegenerative disorder, especially Parkinson disease or an atypical parkinsonian disorder such as corticobasal degeneration.

Truncal dystonia—Truncal dystonia may accompany generalized dystonia, both in children and adults. Isolated or very prominent truncal dystonia at any age should raise suspicion of an acquired or neurodegenerative disorder. In adults, truncal dystonia may lead to forward bending (camptocormia), backward bending (opisthotonus), or sideways bending (Pisa syndrome). Opisthotonus, often combined with retrocollis, is a particularly common manifestation of tardive dystonia due to exposure to dopamine receptor antagonists. Opisthotonus and retrocollis may also occur in young children, and if phasic or paroxysmal can be mistaken for epileptic seizures. It may be the presenting feature or prominent as part of generalized dystonia occurring with encephalitis (29) or several inherited metabolic diseases such as Lesch-Nyhan disease (24), the neurotransmitter disorders and lysosomal storage disorders such as Gaucher disease.

Adult-onset generalized dystonia—Adult-onset generalized dystonia is uncommon and should always raise suspicion of the possibility of an underlying neurodegenerative or genetic cause rather than being idiopathic.

Hemidystonia—Hemidystonia occurring at any age is almost always associated with a contralateral cerebral lesion, usually in the basal ganglia (3).

Combined dystonia syndromes

Dystonia with parkinsonism - Infantile or childhood onset—There have been significant advances in understanding of syndromes which present with infantile or childhood onset dystonia and parkinsonism (30). A disorder of dopamine metabolism always should be considered because of the potential for specific therapy (see Table 3, supplementary materials). Autosomal dominant GTP-cyclohydrolase 1 deficiency (Segawa disease) classically presents in childhood as lower limb dystonia with diurnal variation, but there is a wide spectrum of phenotypes including focal dystonia, paroxysmal exercise induced dystonia, adult onset Parkinson's disease and misdiagnosis as cerebral palsy with apparent corticospinal signs (31, 32). Dystonia dominates and may be the only motor sign in childhood, but parkinsonism becomes more prominent with increasing age. There is usually an exquisite response to small doses of levodopa, but transient early drug-induced symptomatic worsening or dyskinesias, a duration of weeks to months for peak benefit and incomplete therapeutic responses are occasionally encountered (33). The family history may be misleading because of incomplete penetrance and phenotypic variability within a family. The recessively inherited disorders of dopamine metabolism usually present in infancy. The phenotype is usually complex with varying combinations of dystonia (often with oculogyric crises), hypotonia, parkinsonism (including rest tremor of the cranial region, trunk or limbs), pyramidal signs, intellectual delay, and autonomic, sleep or endocrine disturbance (34). The presence of ptosis and facial hypomimia can lead to the misdiagnosis of a muscle disorder. Therapeutic replacement of biopterin or related monoamines may be required. It should be noted that L-aromatic acid decarboxylase deficiency and dopamine transporter deficiency do not respond to treatment with levodopa. A key investigation when a disorder of dopamine metabolism is suspected is measurement of CSF neurotransmitters and pterins (35).

There are other hereditary disorders that present with predominantly childhood-onset dystonia, and in which parkinsonism, when it occurs, typically develops later in the disease course (Table 3, supplementary materials).

Dystonia with parkinsonism - Adolescent and young adult onset—Dystonia with parkinsonism of adolescent and young adult onset has many potential etiologies (Table 4, supplementary materials). Dystonia is three times as more common in sporadic early onset Parkinson's disease (EOPD), affecting 20% of patients with onset <55 years, and another 10% within 2 years of onset (36). Although in most cases parkinsonism will dominate, dystonia of the legs or exercise-induced dystonia can occasionally be the presenting symptom of EOPD.

Dystonia with spasticity +/- parkinsonism (pallidopyramidal syndromes)—Dystonia with spasticity can occur with parkinsonism (pallidopyramidal syndromes, PPS), or without parkinsonism. In the case of dystonia and spasticity without parkinsonism, it is important to determine whether spasticity is the dominant feature and familial (suggesting the possibility of a hereditary spastic paraparesis with dystonia), or whether the dystonia is dominant, which can occur in a number of multi-system neurodegenerative diseases (Table 6, supplementary materials). In 1954, Davison drew attention to the distinct syndromic combination of juvenile or young onset parkinsonism and pyramidal disturbance (37). Since 2006, a number of recessively inherited causes of PPS have been identified, all of which can also manifest dystonia of varying severity (38), although the usefulness of the term PPS has been questioned (39).

One of the most common questions that arises in patients with early onset dystonia combined with spasticity is whether it is due to cerebral palsy. Cerebral palsy itself is a syndrome rather than a disease, implying a static encephalopathy due to an acquired perinatal or early infantile, monophasic cerebral insult. A diagnosis of cerebral palsy is supported by a history of perinatal insult such as intrauterine infection, prematurity or hypoxia, combined with evidence of delayed early motor or speech milestones and typical imaging findings such as ultrasonographic documentation of perinatal cerebral hemorrhage or MRI evidence of early basal ganglia lesions or periventricular leukomalacia. However a history of perinatal insult is absent in approximately 20% of patients diagnosed with dystonic cerebral palsy (40), and the MRI may not show the typical defects. While dystonia is usually present from early childhood, delayed onset dystonia can occur (41).

Dystonia with cerebellar ataxia—There are many diseases in which dystonia and cerebellar ataxia occur together (Table 7, supplementary materials). Many characteristically also involve other motor or non-motor neurological systems, and these additional clinical features provide the clue to the differential diagnosis. However two additional factors strongly influence the differential diagnosis of a patient with dystonia and cerebellar ataxia. Analogous to the situation with dystonia and spasticity, the first, is whether dystonia or ataxia is the dominant motor phenomenology. If ataxia is dominant, then one should focus on the differential diagnosis of ataxias, whereas if dystonia is dominant, one needs to consider a number of multi-system neurodegenerative diseases. The second major consideration is whether the condition is likely to be genetically determined or sporadic.

Many of the spinocerebellar ataxias (SCAs), which are autosomal dominant, can have dystonia as part of their phenotype (42, 43), and occasionally as the presenting feature (44, 45). An autosomal recessive disorder should be suspected if multiple family members in one generation are affected, or if the condition is of young onset. Occasionally, a recessive ataxia can also present with dystonia as the predominant feature (46). Some of these may be treatable, such as Vitamin E deficiency (47).

Dystonia with myoclonus—The term "myoclonic dystonia" was used to describe a syndrome of idiopathic dystonia with prominent myoclonic jerks by Obeso et al. (48). However the presence of dystonia in contemporary and previous reports of autosomal dominant, alcohol responsive hereditary essential myoclonus was recognized soon afterwards (49, 50). The term "myoclonus-dystonia" was proposed in 1998 to emphasize the coexistence rather than dominance of one movement disorder over the other (51). Many kindreds with autosomal dominantly inherited myoclonus dystonia have mutations in the gene for epsilon sarcoglycan (SGCE) (52). Mutation positive patients present in the first 1–2 decades of life, predominantly with myoclonus which is of subcortical origin. Dystonia usually occurs later and remains mild although exceptions occur. The SGCE gene undergoes imprinting so that only 10% of patients who inherit a mutated maternal gene will express the phenotype, and therefore a family history can appear absent. The gene(s) responsible for SGCE-negative families remains unknown, but a number of other known autosomal dominantly and, rarely, recessively inherited (tyrosine hydroxylase mutations (53)) dystonias can have a myoclonus dystonia phenotype (Table 8, supplementary materials).

Myoclonus can also occur as part of a combined dystonia in other diseases. These are usually neurodegenerative disorders and in this setting, the myoclonus is often of cortical origin. Therefore neurophysiological evaluation of the patient with dystonia and myoclonus can be useful.

Dystonia as part of paroxysmal dyskinesia—The diagnosis of any paroxysmal movement disorder can be difficult if the episodes cannot be observed. With modern technology, if the episodes are sufficiently prolonged, patients can be asked to digitally record one or more episodes. If they are too brief or infrequent, then the clinician must rely on the history or precipitation of an attack to make a diagnosis. Once the description of the movements has raised the suspicion that dystonia may be part of the phenomenology, the three most useful characteristics of the attacks that aid in diagnosis are: 1) whether there are specific triggers; 2) the duration of the episodes; and 3) their frequency. The presence or absence of a family history, age of onset and presence of any interictal signs is also of major importance.

The classifications of autosomal dominant paroxysmal choreoathetosis proposed by Lance (54) and later modified and renamed paroxysmal dyskinesia by Demirkiran and Jankovic (55), based on the specific triggers and duration of attacks, have been validated by the discovery of specific genotypes correlating to each of these phenotypes (Table 9, supplementary materials) (56–60). In each syndrome, there is genetic heterogeneity as there are typical kindreds who are negative for the known genes, and conversely at least some sporadic cases are caused by the same gene mutations.

In those with sporadic paroxysmal dystonia, the possibility of an underlying autosomal recessively inherited metabolic or acquired cause needs consideration (Table 9, supplementary materials). However, a psychogenic etiology and acquired disorders such as defects of calcium metabolism or demyelination are also important to consider, because of the need for specific treatment (61).

Dystonia with deafness—In the last 10–20 years, the phenotype and genotype of a number of syndromes with dystonia and deafness have been elucidated (Table 10, supplementary materials). In Mohr-Tranebjaerg syndrome, severe hearing impairment in males is a constant finding and of congenital or infantile onset, but dystonia can develop any time from childhood to late adulthood (62, 63). Rarely, females may have dystonia with only mild deafness (63, 64). Deafness in Woodhouse-Sakati syndrome may be mild or absent (65). Dystonia occurs in approximately 50% of patients and is juvenile-adult in onset (66). Mitochondrial disease should always be considered. Deafness with dystonia is a heterogeneous syndrome and the cause remains unknown in a significant proportion of cases (67).

Dystonia with systemic disease

Isolated or combined dystonia can also be associated with systemic disease, especially endocrine or hematological abnormalities or solid organ involvement (Tables 13–15, supplementary materials).

Syndromes according to brain imaging

Dystonia with MRI findings suggestive of neurodegeneration with brain iron accumulation (NBIA)—The concept of NBIA as a clinical syndrome was first proposed by Hayflick and colleagues (23). In their study of patients diagnosed with possible Hallervorden-Spatz syndrome (renamed pantothenate kinase associated neurological disease, PKAN), two-thirds of those with atypical clinical presentations were negative for mutations in the pantothenate kinase gene. As these patients had increased T2 hypointensity in the globus pallidus suggestive of increased iron content without the eye of the tiger sign (68), they proposed the term NBIA to describe this group for whom the precise diagnosis remained unknown. NBIA is therefore a group of diseases defined by the combination of progressive neurological disease and MRI findings suggestive of increased iron deposition, often involving but not necessarily limited to the globus pallidus. Most patients with NBIA have dystonia as part of their phenotype. In some cases, dystonia is the dominant or presenting feature.

Knowledge of the clinical and radiological phenotype and genetic causes of NBIA has expanded rapidly over the last decade (see Table 16, supplementary materials and Schneider and Bhatia (69) for a recent review). The clinical phenotype of dystonia in NBIA overlaps with that of other causes of dystonia and therefore an MRI with iron sensitive sequences (e.g. T2*, gradient echo) is an essential diagnostic step. The sensitivity of T2 and iron sensitive sequences and range of normality will vary according to age, magnet strength (1.5 or 3.0T) and scanner. Although most of these conditions are rare, many have characteristic findings that can be used to guide genetic testing (70).

NBIA is still an evolving concept. The presence of excess iron deposition in regions identified as having increased MRI T2 hypointensity has been confirmed pathologically in some but not all diseases classified as NBIA, or is not always present even in pathologically or genetically proven cases, raising the question of whether iron deposition is playing a pathogenic role or simply an epiphenomenon (69). Therefore demonstration of MRI evidence of brain iron accumulation in a patient with dystonia is useful in guiding potential genetic diagnosis, but its absence cannot be used to rule out some of the causes of NBIA.

Dystonia with basal ganglia lesions (other than brain iron accumulation)—The demonstration of basal ganglia abnormalities other than brain iron accumulation also has major diagnostic, and sometimes therapeutic, implications. Basal ganglia abnormalities are rarely specific for a particular disease, but the differential diagnosis can be narrowed significantly by taking into account four factors: 1) temporal course of the disease; 2) age of onset; 3) topography of the lesions within the basal ganglia; and 4) signal characteristics of the basal ganglia lesions (see Table 17, supplemental materials). The typical signal characteristics and topography of basal ganglia lesions in different diseases, many of which can manifest with dystonia, has been reviewed in detail (71).

It is beyond the scope of this paper to review every potential cause of dystonia with basal ganglia lesions, but it is important to be aware of the treatable disorders. Wilson's disease can be associated with both hyper- and hypointense lesions on T1 and T2 weighted MRI sequences (72). The diagnosis should be suspected if there is simultaneous involvement of the basal ganglia, thalamus and brainstem (21). Acute demyelinating encephalomyelitis and biotin responsive encephalopathy secondary to mutations in the hTHTR2 (second thiamine transporter) gene (73, 74) are associated with lesions of the basal ganglia and also white and grey matter, and present with acute or subacute encephalopathy accompanied or followed by dystonia in infants, children or adolescents. The aminoacidurias are also characterised by recurrent episodes of acute and subacute encephalopathy followed by the development of symmetrical lesions in the basal ganglia. Glutaric aciduria typically causes striatal lesions whereas methylmalonic aciduria causes pallidal lesions (71). The recognition of these diagnoses is important as they are treated with dietary modification and/or vitamin supplementation (8).

Dystonia with normal brain MRI or atrophy only—A persistently normal brain MRI in the face of significant clinical progression also narrows the etiological possibilities (Table 20, supplementary materials). A normal brain MRI is typical of many forms of genetically determined isolated dystonias, such as DYT1 and DYT6. An MRI that is normal or shows only mild atrophy is typical of certain combined dystonias e.g. Lesch-Nyhan disease, Niemann-Pick type C, and the neuronal ceroid lipofuscinoses.

Specific diagnostic tests in dystonia syndromes

The focus of this paper has been on refining dystonia syndromes in order to narrow the differential diagnosis and guide specific investigations. However it is relatively common to encounter a patient with a progressive, combined dystonia where the clinical, imaging, routine blood or neurophysiological findings fail to point strongly towards a specific

etiological diagnosis. In this setting, a number of additional investigations should be considered. Lysosomal enzyme assays can be performed on blood to diagnose many hereditary metabolic disorders. In a patient with leukodystrophy, serum very long chain fatty acids can reveal the diagnosis of x-linked adrenoleukodystrophy. A urine metabolic screen is required to diagnose many aminoacidurias or urea cycle disorders. Cerebrospinal fluid (CSF) examination for neurotransmitters may provide a clue that one is dealing with a disorder of dopamine metabolism (35), and a low CSF/serum glucose ratio may be the only clue towards a diagnosis of glucose transporter deficiency. Some diseases may require specific assays on fibroblast cultures from skin or other tissue biopsy, such as Niemann-Pick type C or adult onset neuronal ceroid lipofuscinosis (Kuf's disease). Finally, the traditional approach of genetic testing using karyotyping or Sanger sequencing to diagnose specific diseases is increasingly being supplemented by the newer techniques such as CGH (comparative genomic hybridization) microarrays (75), next generation sequencing and the development of gene panels or DNA chips. These new techniques will allow more economical genetic testing to be performed and have the potential to further modify the diagnostic process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Disclosures

Dr Fung: receives a salary from NSW Health, has received research grants from the National Health and Medical Research Council of Australia, and is on Advisory Boards and/or has received travel grants from Abbott/Abbvie, Allergan, Boehringer-Ingelheim, Hospira, Ipsen, Lundbeck, Novartis, Parkinson's KinetiGraph, Solvay and UCB.

Dr Jinnah receives research grant support from the NIH, the Atlanta Clinical & Translational Science Institute, the Dystonia Medical Research Foundation, the Emory University Research Council, and the Bachmann-Strauss Dystonia & Parkinson's Foundation. He also is principal investigator for the Dystonia Coalition, which receives the majority of its support through NIH grant NS065701 from the Office of Rare Diseases Research in the National Center for Advancing Translational Sciences and National Institute of Neurological Disorders and Stroke. The Dystonia Coalition receives additional material or administrative support from industry sponsors (Allergan Inc., Ipsen Biopharm, Medtronic Inc, and Merz Pharmaceuticals) as well as private foundations (The American Dystonia Society, The Bachmann-Strauss Dystonia and Parkinson Foundation, BeatDystonia, The Benign Essential Blepharospasm Foundation, Dystonia Europe, Dystonia Ireland, The Dystonia Medical Research Foundation, The Dystonia Society, The Foundation for Dystonia Research, The National Spasmodic Dysphonia Association, and The National Spasmodic Torticollis Association). Dr. Jinnah has served as a consultant for Psyadon Pharmaceuticals and Savient Pharmaceuticals. He also serves on the Scientific Advisory Boards for the Dystonia Medical Research foundation, Tyler's Hope for a Dystonia Cure, the Lesch-Nyhan Syndrome Children's Research Foundation, and Lesch-Nyhan Action France.

Prof Bhatia has received funding for travel from GlaxoSmithKline, Orion Corporation, Ipsen, and Merz Pharmaceuticals, LLC; serves on the editorial boards of *Movement Disorders and Therapeutic Advances in Neurological Disorders*; receives royalties from the publication of *Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorders* (Oxford University Press, 2008); has received speaker honoraria from GlaxoSmithKline, Ipsen, Merz Pharmaceuticals, LLC, and Sun Pharmaceutical Industries Ltd.; personal compensation for scientific advisory board for GSK and Boehringer Ingelheim; received research support from Ipsen and from the Halley Stewart Trust through Dystonia Society UK, and the Wellcome Trust MRC strategic neurodegenerative disease initiative award (Ref. number WT089698), a grant from the Dystonia Coalition and a grant from Parkinson's UK (Ref. number G-1009).

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Table 1

Diagnostic process in a patient with dystonia.

Phenomenology of the movement disorder(s)

1. Is it dystonia?
2. Is it isolated or combined dystonia?
 - Are there other hyperkinetic components: what kind(s) of involuntary movements are present?
 - Are there hypokinetic components: what is the nature of any impairment of movement?

Dystonia syndrome

1. What is the dominant movement disorder phenomenology?
2. What other movement disorders and other neurological features are present
3. What has been the temporal course of the disease
 - age at onset
 - sequence of development of neurological features
 - tempo of disease
4. What other systemic features are present
5. What does the brain imaging reveal?
6. What are the results of other basic investigations?
7. Are other specialised investigations required? e.g. neurophysiology, urine metabolic screen, CSF examination
8. Classify the patient's dystonia syndrome using the above (see List of Syndromes Table)

Etiological differential diagnosis

1. Generate an etiological differential diagnosis based on the dystonia syndrome
 2. Arrange specific diagnostic tests (e.g. genetic testing, tissue biopsy) based on the differential diagnosis
-

Table 2**Dystonia syndromes****Isolated dystonia syndromes that are red flags for the subsequent development of a combined dystonia syndrome or neurodegenerative disease**

Cranial dystonia in the young adults and children

Adult-onset lower limb dystonia

Adult-onset non-task specific limb dystonia

Truncal dystonia

Adult-onset generalized dystonia

Hemidystonia

Combined dystonia

Dystonia +/- parkinsonism of infantile or childhood onset *

Dystonia +/- parkinsonism of adolescent and young adult onset *

Dystonia and parkinsonism in older adults *

Dystonia with spasticity (+/- parkinsonism) *

Dystonia with cerebellar ataxia *

Dystonia with myoclonus *

Dystonia as part of paroxysmal dyskinesia *

Dystonia with chorea

Dystonia with tics

Dystonia with other neurological involvement

Dystonia with deafness *

Dystonia with ophthalmological abnormalities *

Dystonia with peripheral neuropathy *

Dystonia with progressive dementia (see Progressive dystonia with normal brain MRI)

Dystonia with systemic disease

Dystonia with endocrine abnormalities *

Dystonia with hematological abnormalities *

Dystonia with with solid organ involvement *

Syndromes according to brain imaging

Dystonia with MRI evidence of neuronal brain iron accumulation *

Dystonia with basal ganglia lesions *

Dystonia with leucoencephalopathy *

Dystonia with basal ganglia calcification *

Progressive dystonia with normal brain MRI or generalised atrophy *

* see Supplementary Materials for Table with list of etiologies of this syndrome